[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Arsinic Acids[1]

BY F. F. BLICKE AND G. L. WEBSTER[2]

The object of this paper is to describe the preparation and properties of a number of arsinic acids and their derivatives which were prepared in connection with our study of diarsyls.

By means of an unusual process, namely, treatment of diazotized 2-aminophenylarsonic acid with sulfur dioxide, Kalb[3] obtained a substance which he claimed to be an anhydride of the dihydroxy form of 2-hydroxyphenylarsine oxide, $C_6H_4(OH)As(OH)_2$, but the only experimental evidence offered in support of his structure was an arsenic analysis.

We prepared Kalb's product by means of a more orthodox procedure, that is, hydrolysis of 2-hydroxyphenyldichloroarsine. Both an arsenic analysis and a molecular weight determination offer strong support for the anhydride formula and it seems that this oxide does not exist in the ordinary form $C_6H_4(OH)As{=}O$.

Experimental Part

2- and 3-Aminodiphenylarsinic Acid.—Reduction of 25 g. of the required nitro acid, dissolved in 20 g. of sodium hydroxide and 250 cc. of water, was effected with ferrous hydroxide obtained by addition of 61 g. of sodium hydroxide in 235 cc. of water to 195 g. of ferrous sulfate dissolved in 400 cc. of water. After twenty-four hours the mixture was filtered and the filtrate carefully acidified; yield 15 g. of the 2-amino acid and 16 g. of the 3-amino compound.

2-Hydroxydiphenylarsinic Acid.—A solution, prepared from 27.7 g. of 2-aminodiphenylarsinic acid, 160 cc. of water and 20 cc. of concd. sulfuric acid, was poured onto 400 g. of ice and diazotized with 15.2 g. of sodium nitrite, whereupon a slow evolution of nitrogen began almost immediately. After twenty-four hours the dark brown precipitate of hydroxy acid was filtered; yield 25 g. or 90% of the calcd. amount.

2-Methoxydiphenylarsinic Acid.—A mixture, composed of 5.5 g. of 2-hydroxydiphenylarsinic acid, 20 cc. of water, 5.0 g. of sodium hydroxide and 3.6 cc. of dimethyl sulfate, was shaken until the sulfate had disappeared; the methylation process was repeated four times. The mixture was heated on a steam-bath for one-half hour, partially neutralized with 20 cc. of hydrochloric acid, treated with charcoal and filtered. The cold filtrate was acidified to congo red; yield 5.2 g.

3-Nitrodiphenylarsinic Acid.—A solution, prepared from 27.6 g. of technical 3-nitroaniline, 50 cc. of hydrochloric acid and 100 cc. of water, was diazotized with 13.8 g. of sodium nitrite, dissolved in 400 cc. of water, the mixture then diluted with 1000 cc. of water and treated with 5 N sodium hydroxide until no longer acid toward congo red.

To the stirred diazonium solution, maintained at 15°, there was added, slowly, 33.6 g. of phenylarsine oxide, dissolved in a mixture of 40 cc. of 10 N sodium hydroxide and 180 cc. of water. The mixture was stirred for two hours, made slightly acid with acetic acid, filtered and the filtrate acidified with hydrochloric acid until acid to congo red; the precipitated arsinic acid weighed 16.5 g. The filtrate was neutralized with sodium hydroxide and evaporated to a volume of 300 cc., cooled, made slightly acid with acetic acid, filtered and the filtrate acidified to congo red; 16 g. more of the arsinic acid precipitated; total yield 51% of the calcd. amount.

4-Bromodiphenylarsinic Acid.—A solution of 172 g. of 4-bromoaniline in 350 cc. of hydrochloric acid and 400 cc. of water was poured onto 1000 g. of ice, 1000 cc. of water added and more ice, if necessary to keep the temperature at 0°. The amine was diazotized with 70 g. of sodium nitrite, dissolved in 500 cc. of water.

A solution, prepared from 170 g. of phenylarsine oxide, 160 g. of flake sodium hydroxide and 3000 cc. of water, was added to the diazonium solution during the course of one hour and the mixture was stirred vigorously for three hours. After twelve hours it was filtered. The tarry residue contained 4-chlorobromobenzene. The filtrate was shaken with charcoal, filtered and acidified to congo red with hydrochloric acid; yield 137 g.

3,4′-Dinitrodiphenylarsinic Acid.—The solution, obtained by sifting 30.7 g. of 4-nitrodiphenylarsinic acid[4] onto 100 cc. of concd. sulfuric acid, was cooled to 0°, stirred, and treated, dropwise, with a mixture of 6.4 cc. of nitric acid (sp. gr. 1.42) and 6.4 cc. of sulfuric acid while the temperature was maintained at 0–3°. After twelve hours the mixture was poured onto 700 g. of ice, the yellow, crystalline nitro acid filtered and washed with water; yield 35.0 g.; calcd. yield 35.2 g.

3,4′-Dihydroxydiphenylarsinic Acid.—A solution, prepared from 3.6 g. of 3,4′-diaminodiphenylarsinic acid, 5 cc. of sulfuric acid and 50 cc. of water, was diazotized at 0–5° with 2.0 g. of sodium nitrite dissolved in 10 cc. of water. The mixture was heated for two hours at 55–65°, the liquid decanted from a small amount of red by-product, cooled with ice and stirred. The red gum which separated was discarded. After some time the dihydroxy acid separated from the clear solution in a colorless, crystalline form.

3,3′-Dinitro-4-hydroxydiphenylarsinic Acid.—Twenty-one grams of 4-hydroxydiphenylarsinic acid,[4,5] dissolved in

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[1] This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by G. L. Webster in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

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[3] Kalb, *Ann.*, **423**, 52, 70 (1921).

[4] Blicke and Oneto, THIS JOURNAL, **56**, 685 (1934).

[5] If the solution of diazotized 4-aminodiphenylarsonic acid is heated to 65-70° for one hour, instead of at the boiling point, the yield of 4-hydroxydiphenylarsinic acid is increased to 75% of the calcd. amount.

TABLE I

ARSINIC ACIDS

Compounds 3, 10, 13 and 14 were recrystallized from water, 1, 4 and 11 from 15% acetic acid, 2 and 9 from 40% acetic acid, 5 from 20% alcohol, 6 and 7 from 50% alcohol and 8 and 12 from 85% alcohol. All of the acids are soluble in acetic acid and insoluble in benzene.

		M. p., °C.	Formula	As, %	
				Calcd.	Found
1	2-Aminodiphenyl	129–130[a]	....	...	...
2	2-Hydroxydiphenyl	221–223	$C_{12}H_{11}O_3As$	26.95	26.85
3	2-Methoxydiphenyl	187–188	$C_{13}H_{13}O_3As$	25.65	25.69
4	3-Nitrodiphenyl	154–155	$C_{12}H_{10}O_4NAs$	24.41	24.33
5	3-Aminodiphenyl	210–212	$C_{12}H_{12}O_2NAs$	27.05	27.13
6	3-Hydroxydiphenyl[b]	230–232	$C_{12}H_{11}O_3As$	26.95	26.99
7	3-Methoxydiphenyl[c]	120–121	$C_{13}H_{13}O_3As$	25.65	25.44
8	4-Bromodiphenyl	184–185	$C_{12}H_{10}O_2BrAs$	(23.44	23.60 % Br)
9	3,4'-Dinitrodiphenyl	230–232	$C_{12}H_9O_6N_2As$	21.28	21.41
10	3,4'-Diaminodiphenyl[d]	176–178	$C_{12}H_{13}O_2N_2As$	25.65	25.77
11	3,4'-Dihydroxydiphenyl	210–211	$C_{12}H_{11}O_4As$	25.48	25.76
12	3,3'-Dinitro-4-hydroxydiphenyl	195–196	$C_{12}H_9O_7N_2As$	20.36	20.13
13	Methyl-3-amino-4-hydroxyphenyl[e]	233–234	....	...	...
14	Methyl-3-nitro-4-methoxyphenyl	216–217	$C_8H_{10}O_6NAs$	27.24	27.29

[a] Kalb [*Ann.*, **423**, 60 (1921)] reported the same melting point. [b] For preparative method see corresponding 2-hydroxy compound. [c] For preparative method see corresponding 2-methoxy compound. [d] For preparative method see corresponding 3,3'-diamino compound [Blicke, Oakdale and Oneto, THIS JOURNAL, **56**, 142 (1934)]. [e] Bertheim [*Ber.*, **48**, 358 (1915)] reported 206–207°.

105 cc. of concd. sulfuric acid, was nitrated very slowly with 9.6 cc. of nitric acid (sp. gr. 1.42) and an equal volume of concd. sulfuric acid while the temperature was maintained below 0°. After eight hours the mixture was poured onto 1000 g. of ice and the precipitated acid washed with water; yield 26.5 g. or 95% of the calcd. amount.

Methyl-3-amino-4-hydroxyphenylarsinic Acid.—To 185 g. of technical ferrous sulfate, dissolved in 650 cc. of water, and 200 g. of flake sodium hydroxide, dissolved in 300 cc. of water, there was added 26.1 g. of methyl-3-nitro-4-hydroxyphenylarsinic acid[6] dissolved in a mixture of 100 cc. of water and 10 g. of sodium hydroxide. The mixture was shaken vigorously in a stoppered flask for thirty minutes. After twenty-four hours the material was filtered and the filtrate made acid to congo red by the addition of approximately 280 cc. of concd. hydrochloric acid. The solution was then evaporated to a volume of about 600 cc., filtered, cooled and neutralized to congo red by the addition of sodium hydroxide solution. The amino acid precipitated when the sides of the container were scratched. The product was filtered and a further amount of acid obtained by concentration of the filtrate; yield 16.5 g. or 71% of the calcd. amount.

Methyl-3-nitro-4-methoxyphenylarsinic Acid.—A mixture of 12.2 g. of 3-nitro-4-methoxyphenylarsine oxide, 80 cc. of methyl alcohol, 6 g. of sodium hydroxide (70%) and 45 cc. of water was cooled and shaken with 4 cc. of methyl iodide in a stoppered flask. After twenty-four hours the mixture was filtered and then heated in an evaporating dish until a crust began to form on the surface of the liquid. The material was cooled, diluted with 25 cc. of water and 17 cc. of acetic acid added. The precipitated, crystalline arsinic acid weighed 13.5 g. which is 97% of the calcd. amount; m. p. 216–217° after recrystallization from water.

4-Bromophenylarsonic Acid.[7]—A solution of 172 g. of 4-bromoaniline, 300 cc. of hydrochloric acid and 400 cc. of water was poured onto 800 g. of ice, the mixture stirred and diazotized at 0° with 70 g. of sodium nitrite dissolved in 200 cc. of water. During this process the temperature should remain below 5°.

A mixture of 5 g. of copper sulfate, 50 cc. of water and 10 cc. of ammonia water was added to a solution of 210 g. of sodium arsenite and 250 g. of sodium carbonate in 2000 cc. of water. The mixture was cooled to 15°, stirred vigorously and the solution of the diazotized amine added slowly during the course of one hour. The material was stirred for two hours and after twelve hours was filtered; the filtrate was acidified to congo red with hydrochloric acid; yield 193 g.

4-Nitrophenyldichloroarsine.—One drop of hydriodic acid was added to 10 g. of 4-nitrophenylarsonic acid,[8] dissolved in 25 cc. of hydrochloric acid, the mixture treated with sulfur dioxide and the oily precipitate obtained extracted with benzene. Since the dichloroarsine would not solidify, a crystalline derivative was obtained in the following manner. One-half of the original benzene solution of the dichloroarsine was dried with calcium chloride and treated with the piperidine salt of N-pentamethylene dithiocarbamate.[9] After twenty-four hours the solvent was allowed to evaporate, the crystalline residue washed thoroughly with water and the dried material (8.9 g.) recrystallized from ethyl acetate; m. p. 177–178°. This product was 4-nitrophenylarsylene-N-pentamethylenedithiocarbamate, $(NO_2)C_6H_4As[S—C(S)—NC_5H_{10}]_2$.

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(6) Bertheim, *Ber.*, **48**, 357 (1915).

(7) An inadequately described procedure is found in the German patent 250,264. Mouneyrat (English patent 142,947) prepared the acid by a modified Bart reaction.

(8) Johnson and Adams, THIS JOURNAL, **45**, 1311 (1923).

(9) Blicke and Oakdale, *ibid.*, **54**, 2993 (1932).

TABLE II

ARSINES

	M. p., °C.	Formula	As, % Calcd.	As, % Found	Halide, % Calcd.	Halide, % Found
2-Nitrodiphenyliodo	113–114	$C_{12}H_9O_2NIAs$	18.68	18.77	I 31.66	31.51
2-Aminodiphenylchloro hydrochloride	.....	$C_{12}H_{12}NCl_2As$	...	...	Cl 22.41	22.41
2-Acetylaminodiphenyliodo[a]	147–148	$C_{14}H_{12}ONIAs$	18.14	18.44	I 30.74	30.74
2-Methoxydiphenyliodo[b]	68– 69	$C_{13}H_{12}OIAs$	19.41	19.56	I 32.89	32.84
3-Aminodiphenylchloro hydrochloride[c]	173–175	$C_{12}H_{12}NCl_2As$	23.71	23.79	Cl 22.41	22.51
3-Acetylaminodiphenyliodo[d]	146–147	$C_{14}H_{13}ONIAs$	18.14	17.92	I 30.74	30.86
4-Methoxyphenyldichloro[e]	49– 50[f]	....	...	...	...	...
Methyl-3-amino-4-hydroxyphenylchloro hydrochloride	178–180	$C_7H_{10}ONCl_2As$	27.76	27.63	...	...
Methyl-3-amino-4-hydroxyphenyliodo hydrochloride	136–137	$C_7H_{10}ONI_2As$	16.54	16.74	I 56.06	56.02

[a] Obtained when 5 g. of 2,2″-diacetyldiaminotetraphenylarsyl oxide was warmed with 20 cc. of hydriodic acid for a few minutes. [b] Prepared from 2 g. of 2-methoxydiphenylarsinic acid and 10 cc. of hydriodic acid. [c] Prepared in the same manner as the corresponding 2-amino compound. [d] The compound obtained by acetylation of 3.6 g. of 3,3″-diaminotetraphenylarsyl oxide was rubbed under 35 cc. of hydriodic acid, the acid decanted and 5 cc. of acetic acid added, whereupon the oily iodide became crystalline. [e] Prepared by shaking 5 g. of 4-methoxyphenylarsine oxide with 25 cc. of hydrochloric acid. [f] Michaelis and Weitz [*Ber.*, **20**, 51 (1887)] reported 48°.

Anal. Calcd. for $C_{18}H_{24}O_2N_3S_4As$: As, 14.49; S, 24.79. Found: As, 14.83; S, 24.72.

2-Nitrodiphenyliodoarsine.—Five grams of 2-nitrodiphenylarsinic acid was heated with 20 cc. of hydrochloric acid until the arsinic acid dissolved. A crystalline material, undoubtedly an addition product of the two acids, often begins to precipitate at this stage. After the addition of 5 cc. of water and several drops of hydriodic acid the mixture was saturated with sulfur dioxide. The chloroarsine, which precipitated as a gum, was washed with water. The gum was covered with ether, treated with ammonia water and the arsyl oxide produced dissolved in the ether. The ether solution was separated and the solvent allowed to evaporate. The yellow, crystalline residue (3.6 g.) of the arsyl oxide was pulverized and triturated with excess hydriodic acid. After some time the iodoarsine was filtered on a Jena filter.

2-Aminodiphenylchloroarsine Hydrochloride and 2,2″-Diaminotetraphenylarsyl Oxide.—A mixture of 2 g. of 2-aminodiphenylarsinic acid, 75 cc. of hydrochloric acid and two drops of hydriodic acid was saturated with sulfur dioxide, the precipitated chloroarsine hydrochloride filtered, dissolved in the least possible amount of water and precipitated by the addition of fuming hydrochloric acid.

To obtain the oxide the chloroarsine hydrochloride was dissolved in water, the solution shaken with charcoal, filtered and the filtrate treated with ammonia water, drop by drop, until no more oxide precipitated. The latter was extracted with ether, the solution dried and the solvent removed. The oxide was obtained as a semi-solid mass.

A mixture of 10 g. of the semi-crystalline 2,2″-diaminotetraphenylarsyl oxide and 25 cc. of acetic anhydride was heated until all of the oxide dissolved. White, glistening crystals separated when the mixture was cooled. The product is soluble in alcohol, hot acetone, benzene and acetic acid; m. p. 180–181° after recrystallization from acetic acid.

According to the analyses the acetylated oxide contains acetic acid of crystallization. The three analyses recorded below were made with material prepared at different times.

Anal. Calcd. for $C_{28}H_{26}ON_2As_2 + 1.5CH_3COOH$: As, 22.10. Found: As, 21.97, 22.09, 22.00.

Methyl-3-amino-4-hydroxyphenylchloroarsine Hydrochloride.—A mixture of 5 g. of methyl-3-amino-4-hydroxyphenylarsinic acid, 25 cc. of hydrochloric acid, 15 cc. of water and a drop of hydriodic acid was saturated with sulfur dioxide, the crystalline precipitate dissolved in 25 cc. of warm water, shaken with charcoal, filtered and the chloride hydrochloride precipitated with 25 cc. of hydrochloric acid.

Methyl-3-amino-4-hydroxyphenyliodoarsine Hydriodide.—A solution of 2.6 g. of methyl-3-amino-4-hydroxyphenylchloroarsine hydrochloride in 10 cc. of water was treated with 1.7 g. of sodium bicarbonate, dissolved in 15 cc. of water. The gummy precipitate was triturated with 10 cc. of hydriodic acid (sp. gr. 1.7), the crystalline iodide hydriodide dissolved in 5 cc. of water and precipitated by the addition of 10 cc. of hydriodic acid.

Anhydride of 2-Hydroxyphenylarsine Oxide.—The solution of 2-hydroxyphenylarsonic acid, obtained by coupling 9.3 g. of diazotized 2-aminophenol with sodium arsenite,[10] was made neutral to litmus with hydrochloric acid, filtered, boiled with charcoal, filtered again and acidified to congo red with hydrochloric acid. After several extractions with ether to remove phenol, 1 cc. of hydriodic acid was added and the solution treated with sulfur dioxide. The precipitated, oily dichloroarsine was stirred with 10 g. of sodium carbonate dissolved in water. The thick gum which formed became crystalline when the mixture was heated. After recrystallization from acetone the compound melted at 181–182°.[11]

Anal. Calcd. for $C_6H_4(OH)As{=}O$: As, 40.73; mol. wt., 184. Calcd. for anhydride, $C_{12}H_8O_3As_2$: As, 42.83; mol. wt., 350. Found: As, 42.86; mol. wt., 341.[12]

3-Nitro-4-methoxyphenylarsine Oxide.—Twenty grams of 3-nitro-4-methoxyphenylarsonic acid[13] was dissolved in 1800 cc. of hot water, the solution cooled to 55° and a mixture of 10 cc. of sulfuric acid and 50 cc. of water added. After the addition of 4 cc. of hydriodic acid, sulfur dioxide was led into the hot solution for two hours. After

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[10] Bart, *Ann.*, **429**, 90 (1922).

[11] Kalb [*ibid.*, **423**, 70 (1921)] reported 177°.

[12] Determined by Menzies' method in acetone.

[13] Fargher, *J. Chem. Soc.*, **117**, 865 (1920).

twelve hours the precipitated oxide was filtered; yield 16.5 g. or 94% of the calcd. amount.

The oxide is insoluble in all of the common organic solvents but dissolves in sodium hydroxide solution and precipitates upon the addition of acid. For analysis the crude oxide was washed with hot 10% sodium carbonate solution and then with water until free from sodium carbonate and halides; m. p. 247–248° with decomposition.

Anal. Calcd. for $C_7H_6O_4NAs$: As, 30.84. Found: As, 30.94.

Summary

The preparation of fifteen arsonic and arsinic acids, ten haloarsines and three arsine oxides has been described.

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Diarsyls. VIII. Amino and Hydroxydiarsyls[1]

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It was to be expected that water-soluble tetraaryldiarsyls could be obtained by the preparation of salts of tetraaryldiarsyls which contained nuclear amino or hydroxyl groups. It has been found that 3,3′,3′′,3′′′-tetra-(aminophenyl)-diarsyl[3] forms a water-soluble hydrochloride and that the sodium salts of 4,4″-dihydroxytetraphenyldiarsyl[4] and 3,3′,3′′,3′′′-tetra-(hydroxyphenyl)-diarsyl[4] are soluble in water.

A study of 2,2″-diaminotetraphenyldiarsyl has shown that this substance, dissolved in benzene, separates from the solution when the latter is shaken with concentrated hydrochloric acid in the form of a crystalline, benzene-insoluble compound. When water is added to the mixture the crystalline product dissolves and the diarsyl is found to be present in the benzene layer. This behavior indicates that the hydrochloride of this diarsyl is hydrolyzed extensively by water.

2,2″-Diaminotetraphenyldiarsyl was prepared by two methods: (a) interaction of 2,2″-diaminotetraphenylarsyl oxide with diphenylarsine, a reaction which yields both 2,2″-diaminotetraphenyldiarsyl and tetraphenyldiarsyl: (b) reaction between 2,2″-diaminotetraphenylarsyl oxide and 2-aminodiphenylarsine.

When diphenylarsine was added to 2,2″-dihydroxytetraphenylarsyl oxide, dissolved in benzene, tetraphenyldiarsyl began to precipitate at once but we were not able to isolate the alkali-soluble 2,2″-dihydroxytetraphenyldiarsyl in crystalline form.

2-Methoxydiphenyliodoarsine, dissolved in benzene, reacted rapidly with molecular silver. Although the reaction product could be obtained only in the form of an oil, the halogen-free material seemed to be 2,2″-dihydroxytetraphenyldiarsyl since it decolorized iodine instantly to yield 2-methoxydiphenyliodoarsine.

3,3″-Dihydroxytetraphenyldiarsyl was formed when 3,3′-dihydroxydiphenylarsinic acid was reduced with hypophosphorous acid. The compound is soluble in alkali and reacts rapidly with oxygen when dissolved in an organic solvent.

When 3,3″-dihydroxytetraphenyldiarsyl was methylated with dimethyl sulfate the corresponding 3,3″-dimethoxydiarsyl was produced. This compound also reacts rapidly with oxygen.

A very limited chemical study of dimethyl-di-(3-amino-4-hydroxyphenyl)-diarsyl was made by Bertheim.[5] He treated methyl-3-amino-4-hydroxyphenylarsinic acid with hypophosphorous acid, whereupon the crystalline dihypophosphite of the diarsyl precipitated. He analyzed this compound and stated that it irritates the mucous membrane. Upon treatment of the dihypophosphite with hydrochloric acid a water-soluble dihydrochloride was produced. Bertheim concluded his study of this diarsyl with the analysis of this salt.

We prepared the dihypophosphite of dimethyl-di-(3-amino-4-hydroxyphenyl)-diarsyl in the manner described above, treated the material with sodium hydroxide solution until a clear solution was obtained, acidified the latter with acetic acid and isolated the precipitated diarsyl. The dihydrochloride was prepared from the free base. It was found that this salt, as well as an aqueous, alkaline solution of the diarsyl, absorbed oxygen.

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(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by G. L. Webster in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

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(3) Blicke, Oakdale and Oneto, THIS JOURNAL, **56**, 141 (1934).

(4) Blicke and Oneto, *ibid.*, **56**, 685 (1934).

(5) Bertheim, *Ber.*, **48**, 359 (1915).